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Mathematical Models of the Uptake of Carbon Monoxide on Hemoglobin at Low Carbon Monoxide Levels

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Coburn's differential equation for the uptake of carbon monoxide by hemoglobin and two particular types of solution of this equation were considered and the solutions verified for a group of healthy adults consisting of 73 nonsmoking pedestrians or car passengers exposed to low levels of carbon monoxide as experienced in the city of Lyon. The CO levels at the breathing level and the walking speed of the subjects was continually measured, and the carboxyhemoglobin levels determined at the beginning and the end of each test journey. The values of all the other relevant parameters were also determined. The half-life of carboxyhemoglobin was studied as a function of the degree of activity, the age, the sex and the height of the subjects. Finally a mathematical model was set up to represent a periodic uptake of CO which made it possible to estimate the variations in the carboxyhemoglobin level for any subject during a period of a day or a week without any need to know the initial level.

There is normally a very small concentration of CO in the air as a result of natural phenomena, its level being between 0.01 and 1 ppm. Measurements carried out on the Isle of Sark (*1*), where motor vehicle traffic is prohibited, confirmed that the CO levels were always less than 1 ppm. Measurements made in urban areas in various places in the world over many years have resulted in a considerable quantity of information on CO levels. The exact location where the measurements are made is important, since the highest concentrations are found in the midst of a stream motor vehicles and also inside such vehicles, as confirmed by this investigation. Pedestrians walking along the sidewalks are exposed to a lesser concentration of CO than are motorists. People who are obliged to remain at certain critical locations such as toll booths, garages or in traffic jam in enclosed and poorly ventilated streets are exposed to high CO levels due to road traffic (*2,3*). In order to obtain some idea of the conditions, a person moving within a city will experience CO levels having an average level for the hour in excess of 30 ppm (*4*). American standards for permissible levels to which the public may be exposed are in fact sometimes exceeded (*5,6*).

Dangerous HbCO Level and Particularly Vulnerable Subjects

The effect of carbon monoxide is to reduce oxygenation of the tissues and this effect may be experienced immediately or after a longer period of time. Any increase above the endogenous level can in theory be harmful for a person having an extreme requirement for oxygen, and who cannot compensate a reduced supply of oxygen by physiological means. Such subjects consist mainly of people suffering from coronary atheromatic ischaemia or from cerebral vascular deficiencies. Also at risk

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here are people suffering from pernicious anaemia or from respiratory deficiencies, patients recovering from major surgery or premature babies. Aronow and Isbell (*7*) refers to a "critical" carboxyhemoglobin level of between 0.025 and 0.030 for angina pectoris sufferers, such a level giving rise to an appreciable reduction in the time elapsing before the onset of a painful attack following a given physical effort. The World Health Organization (*5*) estimates that the level for the population exposed to atmospheric pollution should not exceed these limits. In the case of our sample, the 0.025 level was exceeded for 19 out of the 73 subjects (pedestrians or car passengers) as a result of their displacement in the city. However this level can in theory easily be exceeded for subjects remaining in heavily polluted localities. The 0.025 carboxyhemoglobin level would result from an exposure to a 13 ppm CO concentration for more than 24 hr.

Kinetics of the Uptake and Elimination of Carbon Monoxide

Symbols and units used are summarized in Table 1. We used SI units, but for CO concentration used ppm because it is independent of the temperature.

Differential Equation

Coburn et al. (*8*) have proposed the following differential equation (1) for carboxyhemoglobin level as a function of time:

$$V_b\, M[O_2]/Pc_{O_2}\, (1/D_L + P_B - P_{H_2O}/\dot{V}_A)\, d[CO]/dt + [CO] = Pi_{CO}\, M[O_2]/Pc_{O_2} + \dot{V}_{CO}\, M[O_2]/Pc_{O_2}\, (1/D_L + P_B - P_{H_2O}/\dot{V}_A) \quad (1)$$

Numerical Values of the Different Parameters

The values given below are statistical averages for subjects in good health and very different values can apply in individual cases, particularly in the case of subjects suffering from certain diseases. The value of M can vary from 185 to more than 250, and we assumed a value of $M = 250$. $[O_2]$ was given a value such that: $[O_2] + [CO] + [X] = 8.92$ mmole/liter of blood (200 ml/l.) P_B was assumed to have a value of 99.3 kPa (745 mm Hg) for the town of Lyon, which is at an altitude of 120 m above sea level.

Pc_{O_2} and P_{H_2O} were assumed to have values of 13.3 kPa (100 mm Hg) and 6.3 kPa (47.5 mm Hg), respectively.

The value of P_{iCO} is directly related to that of C by the equation: $P_{iCO} = P_B \times 10^{-6}C$. We also assumed that $y = HbCO = 17\,[CO]/[Hb]$, (or $1000\,[CO]/1.316\,[Hb]$, if [CO] and [Hb] are in ml/100 ml and g/100 ml of blood, respectively), and similarly that $HbX = 17\,[X]/[Hb]$. The value of D_L is related to the height and body surface of the subject and the value decreases with age. A number of relationships have been proposed, and the resulting calculated values may differ 20 to 30% for the same subject. We used the following relationships (*9*):

For a man aged 18 or more:

$$D_L = 0.329H - 0.000135Y - 0.318$$

For a woman aged 18 or more:

$$D_L = 0.119H - 0.000087Y - 0.015$$

For a child:

$$D_L = 0.117A - 0.022$$

The value of V_b for adults depends on the sex of the subject and we assumed values of $m/13$ and $m/15$ for male and female subjects, respectively. For children we assumed values of $0.071m$, $0.075m$ and $0.080m$ for 15, 10 and 1-6 year old subjects respectively (*10*).

The value of $\dot{V}_{CO}$ for a standard male subject has been given as 5.2×10^{-6} mmole/sec (0.007 ml/min) (*8*). We assumed that the value varied with the total hemoglobin level $V_b[Hb]$ (for a standard male subject, $V_b = 5$ liters and [Hb] = 155 g/l. blood), giving:

$$\dot{V}_{CO} = 5.2 \times 10^{-6}\, V_b[Hb]/5(155)$$

The degree of alveolar ventilation is proportional (*11*) to the oxygen consumption $\dot{V}_A = 19.63V_{02}$, and this consumption depends in turn on the power expended by the subject (*12*). Thus we have:

$$\dot{V}_A = 4.33 \times 10^{-2}\, P$$

Power Expended

The power expended is the sum of the basal metabolism, the muscular power and the specific dynamic action of the foods: $P = MB + PM + SDA$. The basal metabolism is proportional to the surface area of the body: $MB = Ax$.

Pandolf et al. (*13*) have established an equation giving the rate of energy expenditure for a subject when standing or when walking at different speeds and when carrying or not carrying a load.

$$P\,(SDA = 0) = 1.5m + 2(m + m')\,(m'/m)^2 + e(m + m')\,(1.5V^2 + 0.35\alpha V)$$

Table 1. Symbols and units used.

Symbol	Unit	Definition
A	m^2	Body surface area
$a(t)$		Other form of the coefficient in Coburn's equation
$b(t)$		Other form of the coefficient in Coburn's equation
C	ppm	Carbon monoxide concentration in air
[CO]	mmole/l. of blood	CO level in blood
d		A coefficient depending on the type of meal
D_L	mmole/sec/kPa	Pulmonary CO diffusion capacity
e		A coefficient depending on the condition of ground surface
$f(t)$		Function used for resolving Coburn's equation
$g(t)$		Function used for resolving Coburn's equation
H	m	Height of subject
[Hb]	g/l. of blood	Hemoglobin level
HbCO	fraction	Carboxyhemoglobin level with respect to the total hemoglobin
HbO_2	fraction	Oxyhemoglobin level with respect to the total hemoglobin
HbX	fraction	X hemoglobin level with respect to the total hemoglobin (e.g., nitrosylhemoglobin)
HEL	fraction	Limit endogeneous carboxyhemoglobin level with respect to the total haemoglobin
k	fraction/ppm	A constant for carboxyhemoglobin level
K	fraction/ppm/sec	Rate constant for carboxyhemoglobin formation
K_0	fraction	A coefficient employed in step-by-step calculation: carboxyhemoglobin and oxyhemoglobin levels
K_1	fraction/sec	Coefficient employed in step-by-step calculation: partial rate constant for CO uptake
K_2	$fraction^2/sec$	Coefficient employed in step-by-step calculation: partial rate constant for CO uptake
m	kg	Weight of subject
m'	kg	Load carried by subject
M		Haldane's constant
MB	W	Basal metabolism
$[O_2]$	mmole/l. of blood	Oxygen level in the pulmonary capillaries
p_r		Fraction of the daily energy allowance for one meal
P	W	Total power expended by the subject
P_B	kPa	Barometric pressure
Pc_{CO}	kPa	Average partial CO pressure in the pulmonary capillaries
Pc_{O_2}	kPa	Average partial oxygen pressure in the pulmonary capillaries
P_{H_2O}	kPa	Vapor pressure of water
Pi_{CO}	kPa	Partial CO pressure in inspired air
PM	W	Muscular power (expended)
sda	W	Instantaneous specific dynamic action per 1 kJ of food ingested at last meal
SDA	W	Specific dynamic action of foods
V	m/s	Walking speed
$\dot{V}_A$	mmole/sec	Alveolar ventilation rate
V_b	liters	Blood volume
$\dot{V}_{CO}$	mmole/sec	Rate of endogeneous CO production
V_{O_2}	mmole	Volume of oxygen consumed
w_r	kJ/kg	Heat production to food/kg of body weight
x	W/m^2	Basal metabolism per unit body surface area
[X]	mmole/l. of blood	Possible gas level other than O_2 and CO in the pulmonary capillaries (e.g. nitric derivatives)
Y	years	Age of subject
y	fraction	(= HbCO): proportion of carboxyhemoglobin with respect to total hemoglobin
$\hat{y}(t)$		particular periodic solution of Coburn's equation
y_0	fraction	value of y at time t_0
y_{1m}	fraction	Initial measured value of HbCO
y_{2c}	fraction	Final calculated value of HbCO
y_{2m}	fraction	Final measured value of HbCO
α	per cent	Inclination
δ		Kronecker symbol (1 = standing, 0 = other cases)
τ	sec	Time constant
$\tau_{1/2}$	sec	Half-life

The validity of this equation has been verified for young male subjects of average height and weight (1.75 m, 78.2 kg). The equation gives the value of the total power expended, including the basal metabolism, but for a zero SDA value.

We also considered Scherrer's findings (*12*); he stated that the power expenditure amounts to 1.2 times the basal metabolism for a standing subject and to 1.1 times the same basal metabolism when the subject is sitting and at rest (and 0.9 times when the subject is asleep). We made use of a coefficient d to allow for these factors. Certain authors have shown that a female or an overweight subject expends less energy when at rest as a result of a smaller proportion of muscular tissue which accounts for the difference in metabolism with effort. The additional expenditure of energy as a result of performing work PM is the same (*14*). If we wish to apply the above equation for a subject of either sex then the first term ($1.5m$) in the expression must be a function of the sex. We accordingly replaced the first term by Adx, where x is a function of both age and sex (*15*) and the second term appears only for a stationary, standing subject. We then have:

$$P(\text{SDA} = 0) = Adx + 2\delta(m + m')(m'/m)^2 + e(m + m')(1.5V^2 + 0.35\alpha V) \quad (1)$$

The SDA or additional postprandial heat is defined as the increase in the rate of energy expenditure resulting from the ingestion of a meal, the other conditions being basal. This specific dynamic action varies with time and it rises to a maximum value some 2 hr after the ingestion of a meal (*16*). Furthermore it should be noted that the SDA value depends on the type of food consumed and it can be assumed, as a first approximation, that it is a function of the energy value of the meal, this latter being a function of the age and sex of the subject. It is also proportional to the weight of the individual and we can accordingly refer to w_r, the heat allowance per kilo of weight of the subject. We therefore have:

$$\text{SDA} = mw_r\,(Y, \text{sex})p_r\,\text{sda}$$

where sda is the SDA for 1 kJ of food and p_r is the fraction of the daily energy allowance for each meal.

What is the relative importance of MB, PM and SDA? With our mixed group of subjects made up half of pedestrians and half of car passengers we had values of $\overline{\text{MB}} = 91$, $\overline{\text{PM}} = 80$ and $\overline{\text{SDA}} = 23$. On considering a theoretical subject over a period of one week we obtained average values of MB, PM and SDA of 78, 13 and 17, respectively. Thus the SDA is approximately 20. It represents nearly a quarter of the basal metabolism to which we need to add the muscular work rate which can be greater than the basal metabolism. Thus the SDA is not negligible.

Solving the Differential Equation

Three methods of solving Coburn's equation are considered.

First Method: Step-by-Step Solution. Let y_1 and y_2 be the carboxyhemoglobin levels at times t_1 and t_2, respectively; if C remains unchanged from time t_1 to time t_2 we can write:

$$y_2 = y_1 + (t_2 - t_1)\left\{K_1 - [K_2/(K_0 - y_1)]\right\}$$

where

$$K_0 = \frac{17(8.92 - [\text{X}])}{[\text{Hb}]} \quad (1)$$

$$K_1 = \frac{17}{V_b[\text{Hb}]} \times \left[\frac{Pc_{O_2} + MP_B \times 10^{-6}C}{M\{(1/D_L) + [(P_B - P_{H_2O})/\dot{V}_A]\}} + \dot{V}_{CO}\right] \quad (2)$$

$$K_2 = \left(\frac{17}{[\text{Hb}]}\right)^2 \times \left[\frac{(8.92 - [\text{X}])Pc_{O_2}}{MV_b\{(1/D_L) + [(P_B - P_{H_2O})/\dot{V}_A]\}}\right] \quad (3)$$

The advantage of this method of solving the equation in comparison with the other two methods considered below is that no assumptions need to be made. The disadvantage is that an error is introduced, since no distinction is made between the tangent to the curve and the curve itself at each point.

Second Method: Analytical Solution. If we ignore [CO] (and [X] but it is not strictly necessary) with regard to $[O_2]$, then the basic equation can be put into the form of a linear first order differential equation:

$$(k/K)dy/dt + y = kC + \text{HEL} \quad (4)$$

This is also the form of equation proposed by Chovin and Richalet (*17*) except for the inclusion of

the HEL term, which was based on the results of the experimental investigation by Hanks and Farquhar (*18*). Peterson and Steward (*19*) have verified it for constant concentrations (50 to 200 ppm) in industrial conditions on the whole.

If, in addition, C can be regarded as a linear function of time ($C = at + C_1$) then the analytical solution to the equation becomes:

$$y = \mathrm{HEL} + K\{a[t - (k/K) + C_1\} + \{y_1 - k[a(k/K) - C_1] - \mathrm{HEL}\}\, e^{-Kt/k}$$

where

$$k = \frac{17 \times 8.92 M P_B \times 10^{-6}}{P c_{O_2}[\mathrm{Hb}]}$$

$$K = \frac{17 P_B \times 10^{-6}}{V_b[\mathrm{Hb}]\,[(1/D_L) + [(P_b - P_{H_2O})/\dot{V}_A]}$$

$$\mathrm{HEL} = \frac{17 \times 8.92 M \dot{V}_{CO}}{P c_{O_2}[\mathrm{Hb}]\,[(1/D_L) + [(P_b - P_{H_2O})/\dot{V}_A]}$$

The time constant k/K is then given by:

$$\tau = \frac{8.92M}{P c_{O_2}} V_b \left(\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}_A} \right)$$

The constant k is such that the HbCO level following an infinite time of exposure to a concentration C will be kC + HEL. In particular, the value of k is a function of the hemoglobin level and is independent of the level of activity. The value of the factor K, which defines the rate of uptake of CO by the hemoglobin, increases with the degree of alveolar ventilation and hence with physical activity. Standard values of k and K are listed in Table 3 below. The limit endogeneous carboxyhemoglobin level HEL also increases with the amount of physical activity, but the level remains very low (≤ 0.002).

This analytical method of solving the equation enables us to determine any HbCO level, if the initial level is known, provided the variation of C is linear and K remains constant during the interval concerned, which are not unreasonable assumptions.

Third Method: Periodic Solution. The two methods of solving the differential equation described above depend on a knowledge of the initial HbCO level. This well-established disadvantage can disappear if we ignore [CO] with regard to [O_2] and if the parameters K, C and HEL are periodic functions of time (k being constant for a given subject). It is possible to find a periodic solution by using some analytical properties. For convenience, we use a more mathematical language in this section. If we rewrite the equation

$$dy/dt + a(t)y = b(t)$$

with

$$a(t) = K(t)/k$$

$$b(t) = K(t)\,C(t) + K(t)\,\mathrm{HEL}(t)/k$$

this is a linear differential equation of the first order, whose general solution is

$$y(t) = y_0 f(t) + g(T)$$

with the new functions (*20*)

$$f(t) = \exp\{-\int_0^t a(u)du) \quad f(0) = 1$$

and

$$g(t) = f(t)\int_0^t b(u)/f(u)\, du \quad g(0) = 0$$

If $a(t)$ and $b(t)$ are periodic functions of period T and if $a(t) \geq 0$, it may be easily shown that

$$\hat{y}(t) = g(t)f(t)/[1 - f(t)] + g(t)$$

is a particular solution which is periodic (of period T), and every general solution $y_0 f(t) + g(t)$ converges towards $\hat{y}(t)$ as t is increasing ($t \geq 3$ or $4T$) (*21*). Then the $\hat{y}(t)$ function is a convenient analytical tool to describe the actual variations of the carboxyhemoglobin level $y(t)$ if the data used K,C,HEL are periodic functions of time. So we make the realistic assumption that these data representative of the activity and CO exposure of a person are periodic over a period of 24 hr, or, better, over 7 days; moreover, since these variations are known, it is no longer necessary to measure or to choose arbitrarily the initial HbCO level to describe the variations of the HbCO level in any time interval. In practice, we obtain the values of K, HEL and C every 15 min (during 24 hr or 7 days) and calculate the basal integrals $f(t)$, $g(t)$ at the same moments by numerical methods on a computer.

For the second and third methods, we ignore [CO] with regard to $[O_2]$: the greater the value for HbCO, the more k and HEL are overestimated. We can give $[O_2]$ its initial value $[8.92 - (Hb/17)\ y_1]$ or its mean value. Besides, if we do not ignore [X] when we can estimate it, we must replace 8.92 by 8.92 – [X].

Experimental Verification

In order to validate the theoretical analysis, we carried out tests with a total of 73 subjects whose ages varied from 18 to 60 years and who all stated that they were nonsmokers. This sample was divided into two groups of subjects: one group consisting of car passengers who remained seated in each case for the duration of a test journey within and around the town, and a second group consisting of pedestrians who walked at a nearly constant speed in each case in the actual polluted atmosphere existing in certain streets of the city of Lyon. The pedestrians were accompanied by a technician who ensured that the walking speed was maintained throughout each test journey on making measurements at intervals of 3 to 4 min (the mean speed is 1.09 m/sec).

Samples of blood were taken at the beginning and end of each journey and these samples analyzed in order to obtain values of [Hb], y_{1m} and y_{2m}. The analysis of the blood samples was based on the method developed by Boudene, Godin and Roussel (*22*), where the proportions of hemoglobin and CO in the blood were determined by means of infrared spectroscopy. The carbon monoxide levels in the atmosphere were measured on a continuous basis by means of a polarography technique by using a portable Ecolyser and a paper recorder.

For each of the subjects we had in addition to our knowledge of the values of [Hb], y_{1m}, y_{2m} and C, information concerning the sex, weight, height and age of the subject, the load carried by the subject, the time of day when the subject undertook the test journey and continuous information on the walking

Table 2. Average values of the different parameters for the sample subjects.

Parameter	Men	Women
n	37	36
Age	32	32
[Hb], g/l	147	133
m, kg	71	57
m', kg	3	3
H, m	1.75	1.62
C, ppm	13.9	13.7
V, m/sec	0.70	0.64
Duration, min	126	123
D_L, mmole/sec/kPa	0.190	0.175
A, m^2	1.85	1.59
V_b, liters	5.46	3.78
$V_{CO} \times 10^{-5}$, mmole/sec	5.55	3.49
y_{1m}	0.019	0.018
$\sigma_{y_{1m}}$	0.007	0.006
y_{2m}	0.023	0.021
$\sigma_{y_{2m}}$	0.008	0.006
$\tau_{1/2}$, min		
Activity A	236	208
Activity B	140	117

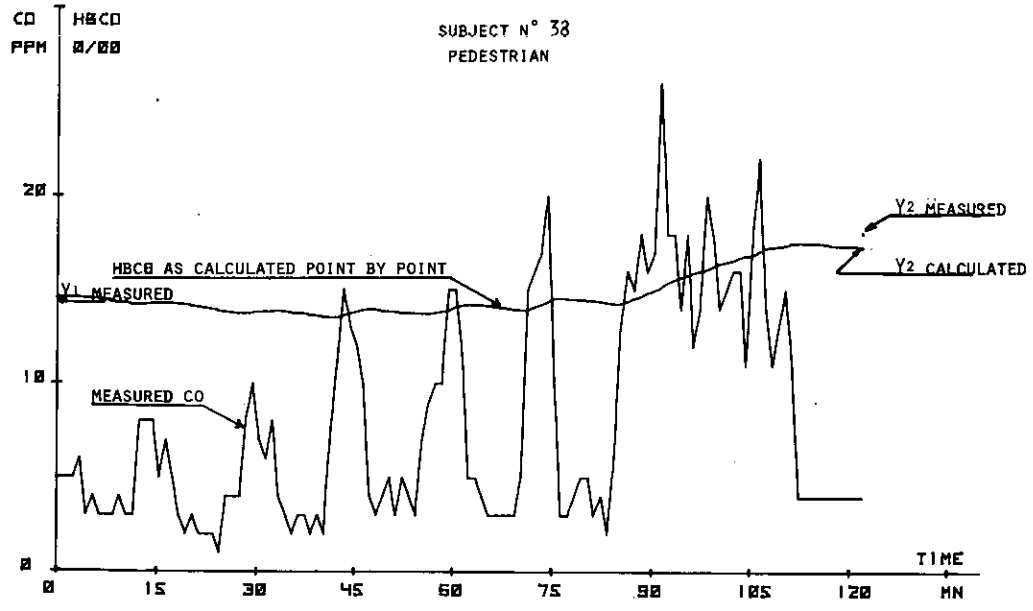

FIGURE 1. Example of an experimental validation of analytical solution.

speed of the pedestrians. Knowing the initial level in each case we calculated the successive carboxyhemoglobin levels throughout the duration of the test and the final level y_{2c} for each subject. An example of the results obtained as a result of making these calculations is given in Figure 1. The calculations were made on using the analytical method without approximate rectification of $[O_2]$ to solve the differential equation and also on using the step by step method on estimating HbX = O or HbX = 0.010. In Table 2 we list with respect to the sex of the subjects, average values of the different parameters for the sample subjects: age, [Hb], m, m', H, CO concentration, V, duration of the tests, D_L, A, V_b, $\dot{V}_CO$, y_{1m}, y_{2m} and the half-life $\tau_{1/2}$ for the subjects when at rest (A) and when walking at a speed of 4 km/hr (B).

As a verification of the validity of the theoretical calculations we compared the final measured levels with the different calculated values. We applied statistical tests to the pairs of values (y_{1m}, y_{2m}), (y_{2m}, y_{2c}) and (y_{2m}/y_{1m}, y_{2c}/y_{1m}) in order to ascertain if there were any significant differences between them (at 5%) for different subsamples as regards the sex and the type of activity. As a result of this it was found that the initial and final measured levels y_{1m} and y_{2m} were significantly different ($p = 10^{-7}$). The method of calculation employed did not have any effect on the results; the differences in the levels determined by each method were not significantly different from one another. There was no significant difference between the calculated and measured levels either for the whole sample of subjects or, except for the case of male pedestrians, for any subsample. This was found for both the (y_{2m}, y_{2c}) and the (y_{2m}/y_{1m}, y_{2c}/y_{1m}) pairs of values. We calculated also Δ = [sign of $(y_{2m}-y_{1m})$] $(y_{2c} - y_{2m})/y_{1m}$, which is positive when the calculated change is too great. Mean Δ showed that the calculated changes were generally lightly too small and in the case of male pedestrians clearly too small.

The calculated results as a whole were very satisfactory for all subjects and particularly so in the case of female pedestrians. Thus we can conclude that the two method (analytical or step-by-step solutions) were equally valid, at least when the level of HbX + HbCO is low. The analytical solution is therefore to be preferred for environmental pollution since it is easier to use; we can give if necessary to $[O_2]$ its initial or mean value. The differential equation for the uptake-elimination of carbon monoxide by hemoglobin and the use of the selected parameter values to model the phenomena is generally valid, although it would appear that the changes in the HbCO levels are underestimated for male pedestrians (the degree of alveolar ventilation is no doubt insufficient in the model).

Applications

Effects on a Particular Subject

The procedure employed to verify the validity of the theoretical approach can also be applied to real life cases. This requires measuring or estimating the CO concentrations throughout the period of time being considered and assuming an initial HbCO level. We can then determine the effects of the changing environment on a real or imaginary subject.

However, it is often difficult, if not impossible, to obtain information on the CO concentration in the air and on the level of activity of the subject at each instant. We must therefore ask what error would be introduced on using average values of CO concentration and/or of the level of activity of the subject? To answer this question let us consider a female subject exposed to an average CO concentration of 15 ppm and walking along at an average speed of 1 m/sec, with both these values varying from zero to twice the average level. The initial level of HbCO is assumed to amount to either 0.010 or 0.050. When calculating the results for this case it was found that no errors are introduced when assuming these average values despite the random variations in the instantaneous values of CO concentration and the level of the subject's activity. In general it was found that only a small error is introduced by assuming an average value for the level of activity but that a significant error can result when assuming an average value for the CO concentration and the period of integration involved is greater than the half-life (see below). The error, however, becomes negligible for periods of integration which are less than the half-life by an order of magnitude or more.

Graphs for Determining the Uptake and Elimination of CO Under Different Conditions

A desk calculator has to be employed to obtain analytical solutions of the differential equation, and we have therefore produced a series of graphs resulting from theoretical calculations which show the way in which CO is taken up or eliminated from hemoglobin for CO concentrations of 0, 10, 30, 50

and 100 ppm for an average (French) women (1.60 m high, 55 kg in weight):

Level of activity A: Subject seated and at rest. $\dot{V}_A$ = 4.06 mmole/ sec = 5460 ml/min

Level of activity B: Subject walking along at a speed of 4 km/hr. $\dot{V}_A$ = 8.87 mmole/sec = (11930 ml/min)

Level of activity C: Subject involved in some strenuous physical or sporting activity such as cycling (at a speed of 15 to 20 km/hr), football or swimming, resulting in a doubling in the value of $\dot{V}_A$ compared to the value for activity B: $\dot{V}_A$ = 17.74 mmole/sec = 23860 ml/min

Two sets of curves are shown on each of these graphs for the different CO concentrations and levels of activity, one set originating from a zero and the other set from a 0.100 HbCO level.

Reference can be made to this graph in determining the approximate fixation-elimination of CO for a subject for a given initial level of HbCO and for continuously varying concentrations of CO in the atmosphere and of levels of activity of the subject. The graphs include curves for each of the three levels of activity for each of the CO concentrations. As an example of the use of these graphs we can consider (see Fig. 2) the case of an average female subject having an initial HbCO level of 0.020 who is successively exposed to different CO concentrations as follows: 30 ppm for 1 hr while at rest, HbCO = 0.028; 50 ppm for 1 hr while walking along at a speed of 4 km/hr, HbCO = 0.049; 0 ppm for 1.5 hr while at rest, HbCO = 0.037; 100 ppm for 1 hr while at rest. On referring to the appropriate graphs for these exposures it will be found that the final HbCO level for the subject amounts to 0.067.

Model of Periodic Conditions

Ott and Mage (*23*) used a simplified point-by-point determination of the HbCO level, CO concen-

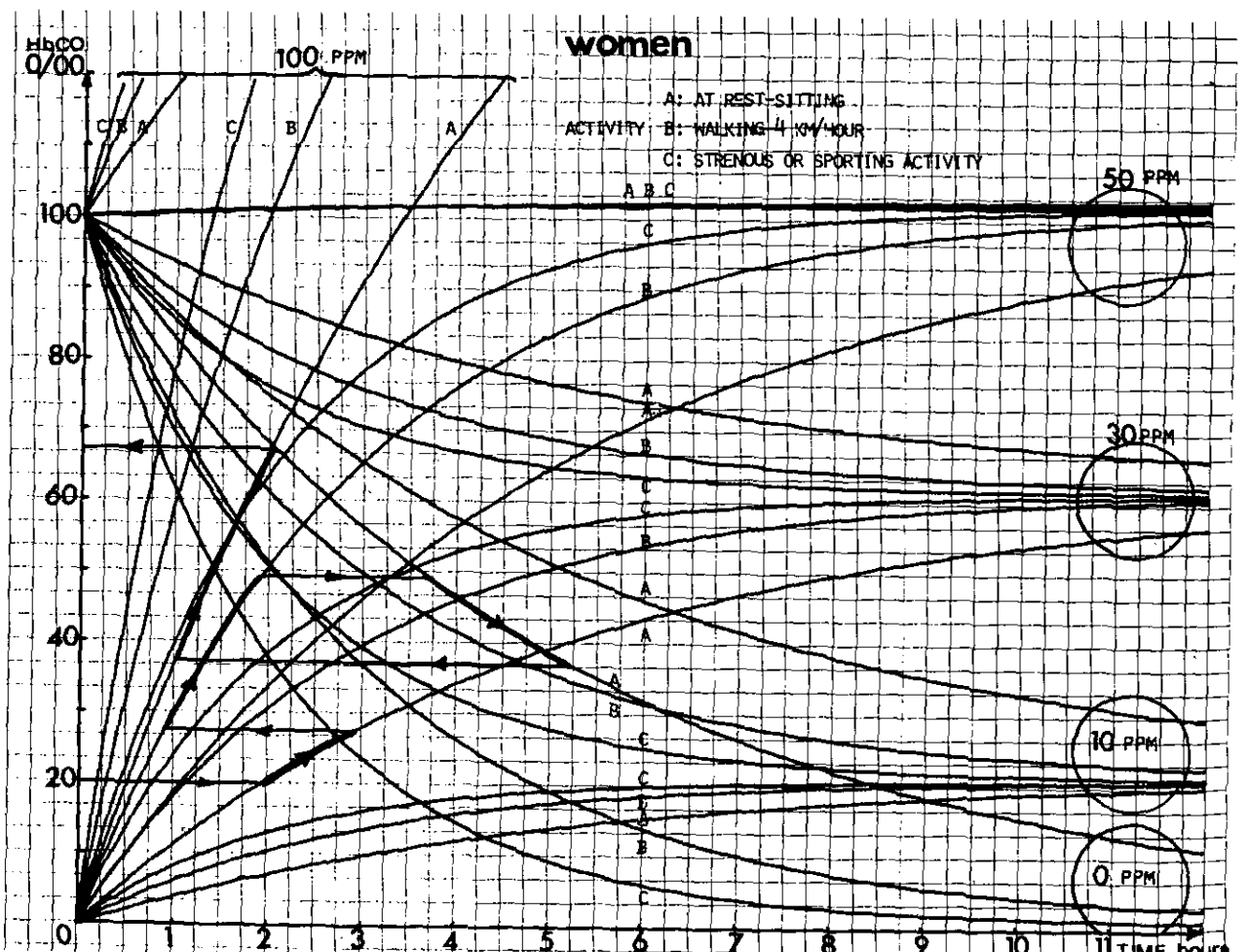

FIGURE 2. Graphs of the uptake-elimination of CO for an average woman, with constant concentration and activity and example of use.

tration being known hour by hour and the physical activity being constant. For a more precise calculation, a point-by-point determination is only possible in the case of relatively short periods of time. For longer periods of time and in cases where the CO concentrations and the levels of activity of the subject vary in a periodic manner it is better if we make use of the periodic method of solving the differential equation. We employed this method for solving the differential equation for two different cases, the time base being a quarter of an hour and the most significant period for the calculations being 1 week. The details of these two cases and the results of the calculations were as follows.

First Case. A customs officer whose place of work was at the side of the road near the French-Swiss frontier lived in the surrounding countryside. The CO concentration at the place of work was measured during the winter of 1978. It was found that the carboxyhemoglobin level varied from 0.002 to 0.033. The level exceeded 0.025 for 3.3% of the total time (corresponding to 14% of the working time) and the average CO concentration (working and rest periods combined) amounted to 3.7 ppm.

Second Case. A saleswoman lived on the outskirts of a large town and worked in a shop located in the main street and in the vicinity of road traffic from Tuesday to Saturday. She travelled to work by bus and spent a part of the weekend in the country. The CO concentrations taken into account were those actually measured at the side-walk of the main street. The CO concentrations in the other locations and the levels of activity taken into account were as estimated. On assuming the subject to be a nonsmoker, it was found that the HbCO level oscillated between values of 0.002 and 0.022. The average CO concentration amounted to 4.7 ppm (Fig. 3).

In order to have some idea of the effects of pollution due to motor vehicle traffic in comparison with the effects of smoking cigarettes (assuming 10 inhalations of 30 ml at 4% CO concentration per

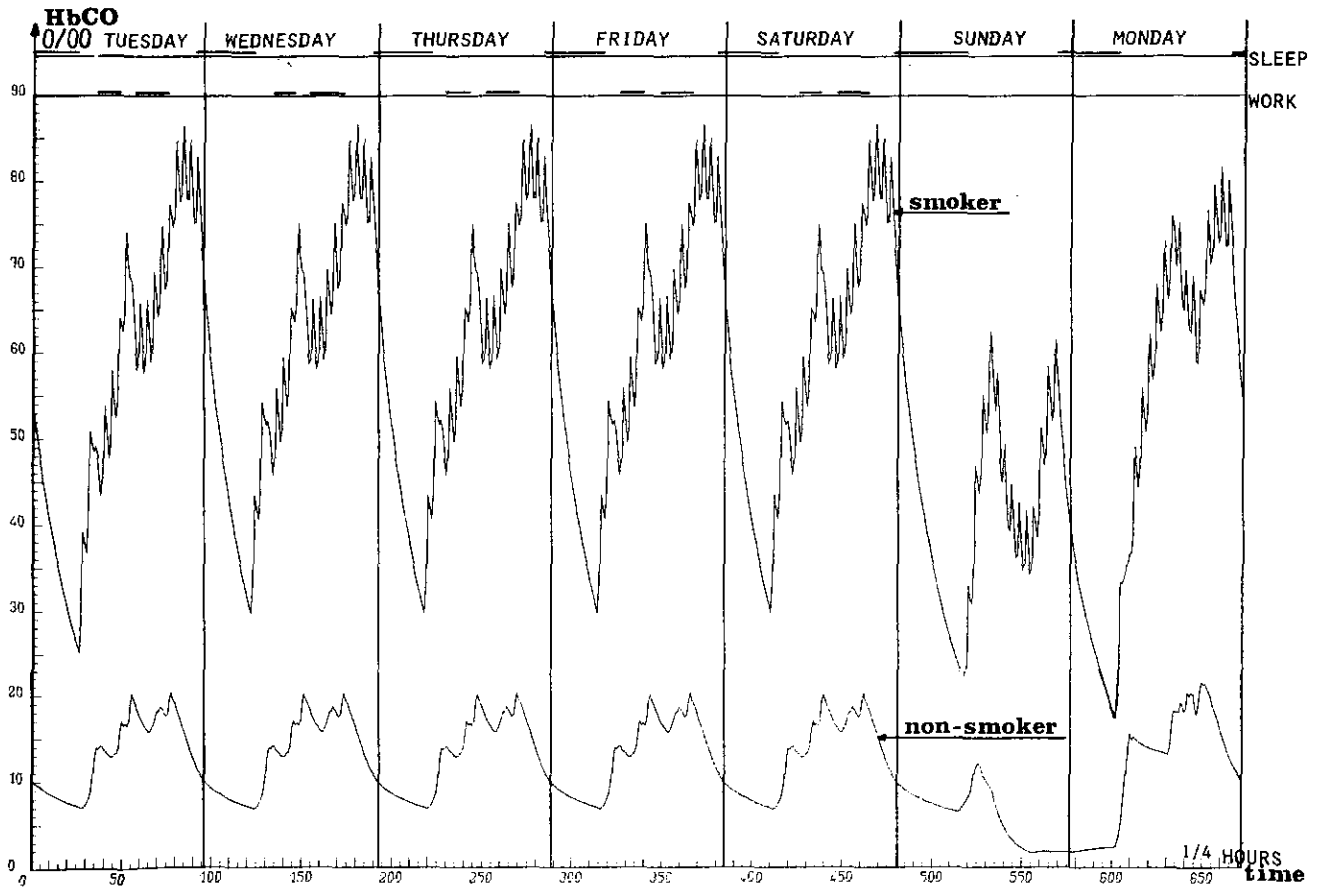

FIGURE 3. Simulation of the periodic variation in HbCO level for a nonsmoking saleswoman and for a subject smoking a total of 103 cigarettes per week.

cigarette) we also considered the case of the same saleswoman smoking at the rate of one cigarette per hour (103 cigarettes per week). The results of the calculations for this case are also shown on Figure 3. The HbCO level oscillated between values of 0.017 and 0.087, while the average CO concentration due to both the motor vehicle traffic and the smoking amounted to 18.3 ppm. The HbCO level exceeded 0.025 for 97% and 0.040 for 79% of the time. The levels were in general some four times greater for the cigarette smoking than for the nonsmoking subject.

The simulation of periodic variations in carboxyhemoglobin levels would appear to be a very useful technique in assessing the effects of carbon monoxide pollution of the atmosphere and of the variations in the actual CO concentration. The calculated HbCO levels given in the examples above are quite consistent with the HbCO levels quoted in the literature (*24-28*). It is necessary, however, to have information on the behavior of the subject on a quarter of an hour to quarter of an hour basis, but there are no problems in making assumptions concerning the behavior of a subject over certain very long periods of time (nighttime and rest periods). It is accordingly possible to determine the effects of any particular variations in CO concentrations during specific periods of time (e.g., during working hours or when travelling). Thus this technique has many potential applications.

Half-life of the Carboxyhemoglobin

Given a constant CO concentration in the air, the time involved for the HbCO level to change from level y_1 to level y_2 is given by:

$$\Delta t = \tau \log \frac{y_1 - \text{HEL} - kC}{y_2 - \text{HEL} - kC}$$

If the atmosphere is unpolluted ($C = 0$) then Δt is the period of time during which the HbCO level decreases from y_1 to y_2. Thus we can determine, for example, the time needed for the HbCO level to fall from 0.200 to 0.010 and from 0.50 to 0.10 for the three standard subjects (male, female and child) and for the previously defined levels of activity A, B and C (Table 3).

If we neglect HEL in the equation for the value of Δt (HEL is always small and is a function of the level of activity of the subject), it then becomes a simple matter to determine the periods of time for the initial HbCO levels to be halved. The times Δt are then independent of the initial and final HbCO levels, and they depend only on the levels of activity of the subjects and the physiological factors involved. Thus we can determine the half-life ($\tau_{1/2} = \tau \log 2$) in each case, this being the period of time for the HbCO level to fall to half of any given value in an unpolluted atmosphere (Table 3). The real half-life is a little lower because we ignore [CO] with regard to [O_2].

The lower the value of $\tau_{1/2}$, the faster will any HbCO level be reduced to one half in an unpolluted atmosphere, and conversely the faster will the new level be doubled in the case of a constant concentration of CO, given that Δt is proportional to τ for such changes in level. The time taken for the HbCO level to double will in fact be proportional to τ (or to $\tau_{1/2}$) the value of this time constant in turn depending essentially on the value of y_2 with respect to the absolute maximum level kC. Thus it would be important to have a good knowledge of half-life. It is interesting to consider what are the population groups (healthy subjects) that are most sensitive to CO pollution in terms of half-life values. The results of the calculations for our sample subjects showed that the standard deviation for the half-life values for either sex amounted to 8%. Thus calculated individual half-life values will deviate appreciable

Table 3. "Standard" values, for 30 year-old men and women and for 6 years-old children, of the constant k, the alveolar ventilation rate $\dot{V}_A$, the rate constant for HbCO formation K, the half-life, the time need for the HbCO level to fall from 0.200 to 0.010 and from 0.050 to 0.010 in unpolluted air, for the levels of physical activity A (at rest-sitting), B (walking 4 km/hour) and C (strenuous or sporting activity).

	Men, k = 0.00183/ppm			Women, k = 0.00202/ppm			Children, k = 0.00223/ppm		
	Activity level A	Activity level B	Activity level C	Activity level A	Activity level B	Activity level C	Activity level A	Activity level B	Activity level C
$\dot{V}_A$, mmole/sec	5.17	10.88	21.77	4.06	8.87	17.74	3.23	5.12	10.25
$K \times 10^{-7}$, fraction/ppm/sec	0.95	1.61	2.35	1.11	1.91	2.75	1.69	2.15	2.81
Half-life $\tau_{1/2}$, min	223	131	90	210	122	85	152	120	92
τ (0.20 → 0.01), min	1030	587	402	973	546	379	706	535	410
τ (0.05 → 0.01), min	575	321	220	543	299	207	494	293	224

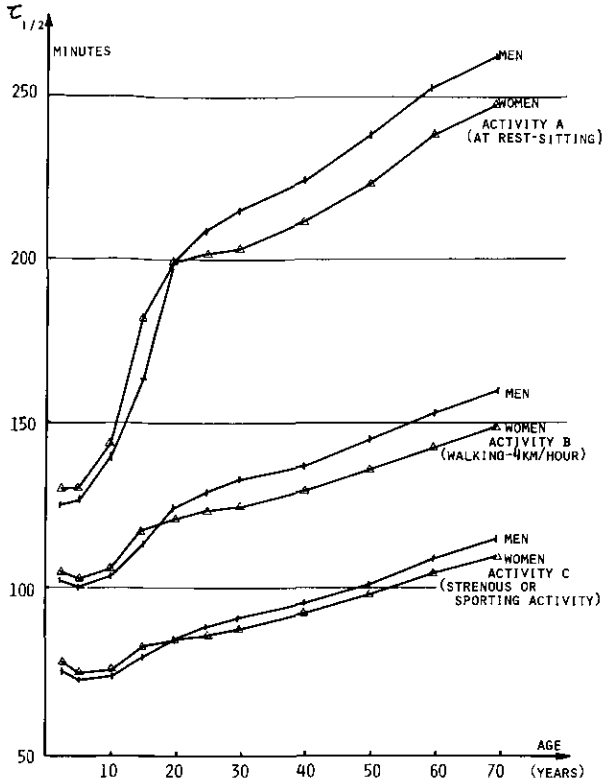

FIGURE 4. Effects of age and the level of physical activity on HbCO half-life.

from the average and the actual deviation will be even greater in the case of the actual population.

The half-life increases with age, the increase being rapid up to the age of 20 years, after which the increase with age slows down (Fig. 4). Age has a greater effect on the half-life than does the sex of the subject. Thus it may be seen from Figure 4 that the half-life for subjects at rest doubles as the age increases from 2 to 70 years, whereas the difference in half-life between male and female subjects does not exceed 6%. The half-life decreases with physical activity, the effect here being about the same for both male and female subjects but less pronounced for children where the muscular power expended is a small proportion of the total power expended. The degree of variation in the half-life with age or the sex of the subject decreases as the level of activity increases. We also studied the effect of the height on the half-life in the case of healthy subjects whose weight was an optimum with respect to height according to the relationship: $m = 75H + 0.25Y - 67.5$ for a male subject, the weight being assumed to be 5 to 10% less for a female (*29*). Height had only a slight effect on half-life in the case of female subjects involved in a low level of activity, when $\tau_{1/2}$ was found to increase with height.

Conclusions

The uptake-elimination of carbon monoxide by hemoglobin, i.e., the variation in the level of carboxyhemoglobin (HbCO) of a subject, can be defined by a fairly complex differential equation which involves a number of physiological parameters. We verified the validity of this equation on a sample of 73 subjects made up of persons of both sexes, and for different levels of physical activity and low carbon monoxide levels. As a result of our tests on these sample subjects we established the validity of two methods of simulating the uptake-elimination of carbon monoxide which take account of the nonpathologic variations for individual subjects. Thus the HbCO levels at each instant of a given period of time (day, week, etc.) can be predicted with reference to initial level and on taking account of the applicable conditions as a result of an analytical method of solving the differential equation (actual calculations in each case or use of an existing set of graphs based on previous calculations). This can be done better by a mathematically based simulation of the periodic variations in HbCO levels without reference to initial level. The HbCO levels depend first of all on the CO concentration in the atmosphere and then on the level of physical activity, the age (the half-life increasing with age) and finally on the sex (the half-life is a little shorter for the female sex) of the subject.

It would appear that the HbCO levels predicted by the periodic simulation are a function of the HbCO half-life (as determined by a fairly simple calculation) but this matter should be the subject of a more systematic statistically based study.

Although we did not study the matter in any detail, it appears that subjects suffering from certain ailments and in particular from respiratory deficiencies for whom certain physiological variables deviate appreciable from the normal values can have carboxyhemoglobin levels that are significantly different from those encountered in the course of this investigation. We need more detailed information for such cases.

It is difficult to reach any conclusion with regard to the short-term and long-term effects of the low carboxyhemoglobin levels that have been observed in a nonsmoking population. With the exception of people who are exposed to the atmospheric pollution due to road vehicle traffic, in particular because of their occupation, it appears however that there are no effects on either the alertness or sensory perception of pedestrians or car passengers making journeys of short duration in the city of Lyon. For the car passengers in our sample, who

were the subjects exposed to the highest level of atmospheric pollution, the HbCO level amounted to 0.027, on the average, at the end of their test journey. The levels of atmospheric pollution normally encountered can however have effects on advent of arteriosclerotic lesions. Thus such levels are sufficient to result in the occurrence or an increase in the seriousness of acute ischaemic incidents in subjects who already suffer from artery deficiencies.

Apart from being useful in establishing carbon monoxide atmospheric pollution indices, the results of this study may also contribute to the establishment of the standards for acceptable carbon monoxide concentrations on the basis of the following approach: establish the carboxyhemoglobin levels that must not be exceeded for both healthy and pathological subjects; determine the CO concentrations that are in agreement with these carboxyhemoglobin levels by simulating the cyclic variations as well as employing other techniques.

In making this approach, it must be understood that there is no such thing as a population of average subjects, but the physiological characteristics and hence the sensitivity to the effects of carbon monoxide vary in accordance with a Gaussian distribution about the mean values that we have considered here for healthy subjects. There is also the fact that there are pathological variations of physiological data for a significant proportion of the population.

More generally, the results of the study can be of use whenever it appears to be necessary to give proper attention to certain periods of time that are being studied out of their normal context (e.g., in the case of industrial medicine studies periods of time, other than the concerned with work high carbon monoxide concentration considered periods, could affect carboxyhemoglobin levels), first for low pollution, because the precision of certain methods is a good as low is HbCO level.

This study has been the subject of an internal report (*30*).

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